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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,695	03/19/2004	Rosa Cuberes Altisen	785-011732-US (PAR)	9152

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EXAMINER	
NOLAN, JASON MICHAEL	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 05/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,695	ALTISEN ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are currently pending in the application. **Claims 1-9** stand rejected and **Claims 10-12** are withdrawn from further consideration. No amendments to **Claims 1-9** have been presented.

Response to Claim Rejections

Applicant's traversal of **Claims 1-9**, rejected under 35 U.S.C. § 103(a) is acknowledged. **Claim 1** contains compounds according to the formulae I and I', **Claim 7** relates to formula I, **Claims 2-6 and 8** are related to formula I', and **Claim 9** pertains to both formulae.

With respect to the **Claims 1 and 7**, Applicants state that it is the Examiner's opinion that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent any unexpected results; and disagree with the view of the Examiner regarding said substitution even in the absence of any unexpected results. Applicant's claim of unexpected results include the theory that a methyl radical is far more electron rich and sterically demanding than a hydrogen radical, and two methyl substituents about a phenyl ring alter the electronic properties of the phenyl ring with respect to mesomeric and inductive effects. Furthermore, Applicants state that the prior art of Cuberes-Altisent *et al.* does not describe how the phenyl ring has to be modified to obtain pharmacologically active compounds whereas the subject matter sought to be patented in the claims are "surprisingly pharmacologically active". Inasmuch, Applicant's state that there is no hint in the prior art that the pyrazoline compounds described therein show any activity in the treatment of cancer, whereas the

compounds of the instant application show good activity in vitro. Applicants state that the similar activity between the compounds of the prior art and those of the instant application do not provide motivation to make the claimed compounds.

No specific arguments are presented with respect to formula I' regarding the positional differences between the prior art and the instantly claimed compounds. Response to these arguments is presented in the following rejection.

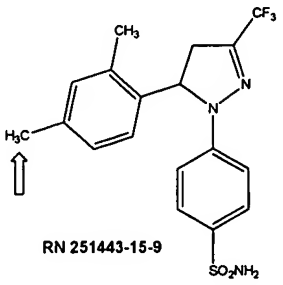
Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

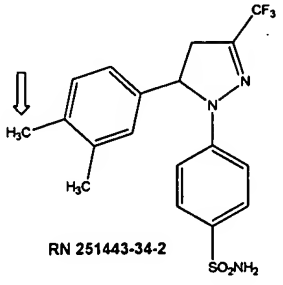
Claims 1-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cuberes-Altisent *et al.* (WO 99/62884, **1999**, see US Patent 6,353,117), taken alone.

Determination of the scope and content of the prior art (MPEP § 2141.01)

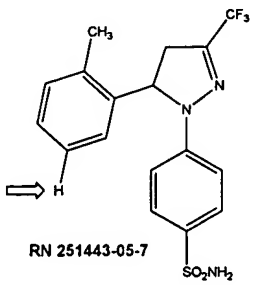
Cuberes-Altisent *et al.* teaches the following compounds shown below:



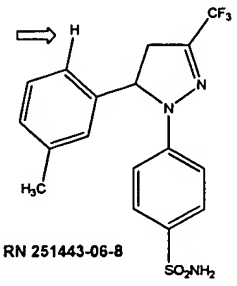
RN 251443-15-9



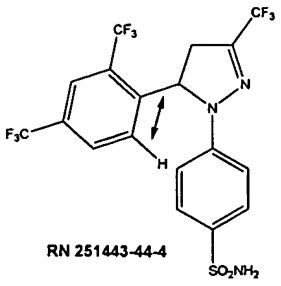
RN 251443-34-2



RN 251443-05-7



RN 251443-06-8



RN 251443-44-4

These compounds taught by Cuberes-Altisent *et al.* are useful for the treatment of inflammation, neoplastic disorders, and angiogenesis-mediated disorders. At the time the instant application was filed (March 2004), it was known in the field that COX-2 inhibitors showed potential for the treatment of cancers via reducing cancer cell proliferation and inducing cancer cell apoptosis, (Fosslien, E.; *Annals of Clinical & Laboratory Science*, **2000**, Vol. 30, Issue 1, p. 3-21). Compounds in this prior art were shown to demonstrate selective inhibition of COX-2, see Tables 3 and 4 (column 27 in US Patent 6,353,117). It is also pointed out that the WO 99/62884 abstract of Cuberes-Altisent *et al.* explicitly states that the compounds of the prior art are useful for the treatment of neoplastic disorders and angiogenesis-mediated disorders (cancer).

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

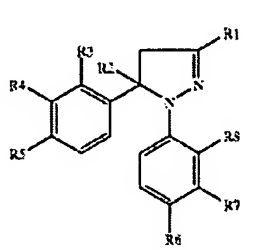
The difference between the prior art of Cuberes-Altisent *et al.* and the compounds of formula I in the instant application are pointed out in the scheme above, which show the positioning of the methyl substituents on the phenyl ring (all with respect to the heterocyclic substituent). Formula I of the instant application is substituted at the ortho(2)- and meta(5)-positions of the phenyl. Compounds RN 251443-15-9 and RN 251443-05-7 have ortho(2)-position methyl groups and compounds RN 251443-34-2 and RN 251443-06-8 have meta(5)-position methyl groups. The arrows indicate that there is either a hydrogen in the spot where a methyl is for formula I (RN 251443-05-7 and RN 251443-06-8) or where the methyl group is in a different position than in formula I (RN 251443-14-9 and RN 251443-34-2).

The difference between the prior art of Cuberes-Altisent *et al.* and the compounds of formula I' in the instant application is the positioning of the phenyl substituent. In formula I' of the instant application, both R_3 and R_4 are meta with respect to the heterocyclic ring and are limited to being, equal or different, a C_{1-6} alkyl group, of which at least one is substituted with at least one halogen. Compound RN 251443-44-4, taught by Cuberes-Altisent *et al.* meets this criterion, with the exception that it is a positional isomer, such that the CF_3 groups are ortho- and para- to the heterocyclic substituent. The arrow indicates the positional difference between this compound and the compounds of formula I'.

Therefore, the teachings of Cuberes-Altisent *et al.* disclose every feature of the subject matter sought to be patented in **Claims 1-9** for both formula I and I' except that the claim recites substituent groups R^1, R^2, R^3, and R^4, which may be methyl or trifuoromethyl, whereas Cuberes-Altisent *et al.* discloses a hydrogen instead of R^2 in formula I and a positional difference between R^3 and R^4 on the phenyl ring and the heterocyclic ring that the phenyl is attached to in formula I'.

The teachings of Cuberes-Altisent *et al.* include the substituents methyl and trifluoromethyl (among others) for R3, R4, and R5 in **Claim 1** of US Patent 6,353,117, shown below, and therefore describe how the phenyl ring has to be modified for pharmacological activity.

What is claimed is:
1. A derivative of pyrazoline of formula (I)



(I)

wherein:
R_1 represents hydrogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, carboxylic acid, lower carboxylate of 1 to 4 carbon atoms, carboxamide or cyano group;
R_2 represents a hydrogen or methyl group;
R_3, R_4, R_7 and R_8, are the same or different, represent hydrogen, chlorine, fluorine, methyl, trifluoromethyl or methoxy group;
R_5 represents hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulfonyl, aminosulphonyl or acetylaminosulphonyl group;

Finding of prima facie obviousness--rational and motivation (MPEP § 2142-2413)

One skilled in the art would have found the claimed compound (formula I) *prima facie* obvious because it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). One skilled in the art would have found the claimed compound (formula I') *prima facie* obvious because it is well established that nothing unobvious is seen in substituting the known claimed isomers, as taught by Cuberes-Altisent *et al.*, since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. *In re Norris,* 84 USPQ 458 (1950).

Additionally, based on a careful review of the cited reference, it was found that Cuberes-Altisent *et al.* discloses a similar method of making the prior art compounds,

and similar properties possessed by those compounds, compared with the instantly claimed compounds. Under these circumstances, considering the close structural similarity between the claimed and prior art compounds, the similar method of making the respective compounds, and the similar properties of those compounds, it is concluded that the claimed compounds would have been *prima facie* obvious in view of the cited prior art.

Applicants' main argument is that a methyl radical is far more electron rich and sterically demanding than a hydrogen radical, and two methyl substituents about a phenyl ring alter the electronic properties of the phenyl ring with respect to mesomeric and inductive effect. The Examiner points out that these statements are not evidence of unexpected results, but of the opinion of the Applicant. Although the substitution of a methyl for a hydrogen may change the mesomeric and inductive effects of an aromatic system, the change would be minute and the structural changes do not overcome the precedent of the case law established above. However, for completeness, shown below are the properties of the instantly claimed compounds and those of the prior art: RN 251443-15-9 (example 24 in column 21) and RN 251443-44-4 (example 54 in column 23) are compared to Example 1 (formula I) and Example 2 (formula I') on page 16 of the Specification.

Table 2 from US Patent 6,353,117:

TABLE 2-continued

Example	m.p. °C.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ ppm
24	158–160	3361, 3270, 1593, 1325, 1168, 1140, 821	2.3(s, 3H); 2.4(s, 3H); 2.9(dd, J=6.9, 17.7Hz, 1H); 3.8(dd, J=12.9, 17.7Hz, 1H); 4.7(broad s, 2H); 5.6(dd, J=6.9, 12.9Hz, 1H); 6.8–7.0(m, 4H);
54	212–4	3376, 3277, 1597, 1332, 1274, 1132	2.8(dd, J=6.3, 18.5Hz, 1H); 3.7(dd, J=13, 18.5Hz, 1H); 5.75(dd, J=6.3, 13Hz, 1H); 6.1(s, 2H); 6.8(d, J=8.5Hz, 2H); 7.2(d, J=8.3Hz, 1H); 7.6(d, J=8.5Hz, 2H); 7.65(d, J=8.3Hz, 1H); 7.9(s, 1H)

Table 2 from instant application (Specification):

TABLE 2

Example	m.p.(°C)	IR (KBr, cm^{-1})	^{1}H-RMN ($CDCl_3$, δ)
1	200-202	3385,5, 3274,7, 1594,3,1327,8, 1149,1	2,1 (s, 3H), 2,3 (s, 3H), 2,84 (dd, J=6,8 y 12,8 Hz, 1H), 3,9 (dd, 12,8 y 13,2 Hz, 1H), 5,8 (dd, J=6,8 y 13,2 Hz, 1H), 6,7 (s, 1H), 6,9 (m, 3H), 7,1 (m, 1H), 7,6 (d, J=8,9 Hz)
2	195-197	3362, 3264, 1597, 1509, 1334, 1279, 1136, 903.	1,8 (bs, 2H), 3,0 (dd, J=7,1 y 17,8 Hz, 1H), 3,8 (dd, J=12,9 y 17,8Hz, 1H), 5,5 (dd, J=7,1 y 12,7 Hz, 1H), 6,95 (d, J=8,8 Hz, 2H), 7,65 (s, 2H), 7,7 (d, J=8,8 Hz, 2H), 7,8 (s, 1H)

As shown in the tables above the compounds of the instant application (bottom table) have very similar properties as those of the prior art (top table). The tables include melting point, IR, and most importantly NMR data. The NMR values shown above for the corresponding hydrogens on the compounds of concern are very similar, proving that that the electronic fields of which they are a part of are similar. For example, in formula I, there are two methyl groups on the tri-substituted phenyl ring with NMR peaks at 2.1 and 2.3 ppm, whereas in example 24 of the prior art, the two methyl groups are 2.4 and 2.3 ppm; a small shift (0.3 ppm) resulting from the positional difference.

The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (i.e. pharmacological use, and more specifically, the treatment of cancer). In this case, Applicants present in *vitro* data showing that examples 1 and 2 have antitumoral activity (Table 3 of Specification, page 17). It is also recited under Table 3 that "The compounds of Examples 1 and 2 do not display any inhibiting activity of enzymes COX-1 and COX-2," however, no testing experiments or data is provided to support that statement. As stated previously, the compounds of Cuberes-Altisent *et al.* are useful for the treatment of inflammation, neoplastic disorders, and angiogenesis-mediated disorders; it was known in the field that COX-2 inhibitors showed potential for the treatment of cancers; and one of skill in the art, with such knowledge, would be motivated to make structurally similar compounds for the treatment of cancer (whether or not they share the same biological mechanism, i.e. inhibition of COX-2 enzymes) with an expectation of success.

Conclusion

Applicant's arguments filed 4/13/2006 have been fully considered but they are not persuasive because Applicant has not submitted objective evidence of non-obviousness sufficient to rebut the *prima facie* case. Accordingly, the claimed subject matter, considered as a whole, would have been obvious within the meaning of 35 U.S.C. § 103(a) based on the disclosure of Cuberes-Altisent *et al.* In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long

as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: May 22, 2006